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THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Marc Feldmann and Ravinder N. Maini
Serial No. : 09/921,937 Examiner: Not yet known
Filed : August 3, 2001 Group Art Unit: Not yet known
For : ANTI-TNF ANTIBODIES AND METHOTREXATE IN THE
TREATMENT OF AUTOIMMUNE DISEASE

1185 Avenue of the Americas
New York, New York 10036
November 26, 2001

Hon. Commissioner for Patents
P.O. Box 2327
Arlington, Virginia 22202

Sir:

INFORMATION DISCLOSURE STATEMENT

Applicants submit herewith an Information Disclosure Statement under 37 C.F.R. §1.56.

In accordance with their duty of disclosure under 37 C.F.R. §1.56 and 37 C.F.R. §1.97(a)-(b)(2), applicants would like to direct the Examiner's attention to the following publications which are listed on the attached Form PTO-1449 (**Exhibit A**). Copies of cited publications 1-5 and 12 are attached hereto as **Exhibits 1 - 6**, respectively. Publications 6-11 and 13-60 were entered in prior application U.S. Serial No. 08/690,775 (filed August 1, 1996), to which priority under 35 U.S.C. §120 is claimed. According to 37 C.F.R. §1.98(d), copies of patents or publications that were previously cited by, or submitted to, the Office in connection with such prior applications need not accompany the Information

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Disclosure Statement.

1. U.S. Patent No. 6,015,557, issued January 18, 2000 (Tobinick et al.) (**Exhibit 1**);
2. U.S. Patent No. 6,177,077 B1, issued January 23, 2001 (Tobinick) (**Exhibit 2**);
3. U.S. Patent No. 5,795,967, issued August 18, 1998 (Aggarwal et al.) (**Exhibit 3**);
4. U.S. Patent No. 5,958,413, issued September 28, 1999 (Anagnostopulos et al.) (**Exhibit 4**);
5. U.S. Patent No. 6,190,691 B1, issued February 20, 2001 (Mak et al.) (**Exhibit 5**);
6. U.S. Patent No. 5,656,272, issued August 6, 1997 (Le et al.);
7. U.S. Patent No. 5,741,488, issued April 21, 1998 (Feldmann et al.);
8. U.S. Patent No. 5,698,195, issued December 16, 1997 (Le et al.);
9. U.S. Patent No. 5,919,452, issued July 6, 1999 (Le et al.);
10. U.S. Patent No. 5,317,019, issued May 31, 1994 (Bender et al.);

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11. U.S. Patent No. 5,672,347, issued September 30, 1997 (Aggarwal et al.);
12. PCT Publication No. WO 00/50079, published August 31, 2000 (Exhibit 6);
13. PCT Publication No. WO 92/08474, published May 29, 1992;
14. PCT Publication No. WO 92/07585, published May 14, 1992;
15. PCT Publication No. WO 92/16553, published October 1, 1992;
16. PCT Publication No. WO 95/09652, published April 13, 1995;
17. PCT Publication No. WO 96/33204, published October 24, 1996;
18. PCT Publication No. WO 98/24463, published June 11, 1998;
19. PCT Publication No. WO 89/08460, published September 21, 1989;
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21. Bologna, C., and Sany, J., "Association des Traitements de Fond dans la Polyarthrite Rhumatoide," *Presse Med.*, 25:876-878 (1996);
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Baillière's Clin. Rheum., 9(4):689-710 (1995);

23. Brahn, E. et al., "Effects of Tumor Necrosis Factor and Combination Cyclosporine A/Methotrexate Therapy on Collagen Arthritis," *Arthritis & Rheumatism*, 32 (Suppl. 4):S133 (1992), Abstract D42;
24. Breedveld, F., et al., "Anti-CD4 Antibodies in Rheumatoid Arthritis," *Clinical and Experimental Rheumatology*, 10(4):325-326 (1992);
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31. Elliott, M.J. et al., "Treatment of Rheumatoid Arthritis with Chimeric Monoclonal Antibodies to TNF- α : Safety, Clinical Efficacy and Control of the Acute Phase Response," *Cell. Biochemistry, Supplement*, 0(17B):145 (1993); Abstract EZ405;
32. Elliott, M.J. et al., "Treatment of Rheumatoid Arthritis with Chimeric Monoclonal Antibodies to TNF α ", *Rev. Esp. Rheumatol*, 20 Suppl. 1:148 (1993); Abstract 320;
33. Elliott, M.J., et al., "Treatment of Rheumatoid Arthritis with Chimeric Monoclonal Antibodies to Tumor Necrosis Factor α ," *Arth. Rheum.*, 36(12):1681-1690 (1993);
34. Elliott, M.J., et al., "Randomised Double-Blind Comparison of Chimeric Monoclonal Antibody to Tumor Necrosis Factor α (cA2) Versus Placebo in Rheumatoid Arthritis," *The Lancet* 344:1105-1110 (1994);
35. Elliott, M.J., et al., "Repeated Therapy with Monoclonal Antibody to Tumor Necrosis Factor α (cA2) in Patients with Rheumatoid Arthritis," *The Lancet* 344:1125-1127 (1994);

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36. Hervé, P., et al., "Phase I-II Trial of a Monoclonal Anti-Tumor Necrosis Factor α Antibody for the Treatment of Refractory Severe Acute Graft-Versus-Host Disease," *Blood*, 79:3362-3368 (1992);
37. Horneff, G., et al., "Elevated Levels of Circulating Tumor Necrosis Factor- α , Interferon- γ , and Interleukin-2 in Systemic Reactions Induced by Anti-CD4 Therapy in Patients with Rheumatoid Arthritis," *Cytokine*, 3(3):266-267 (1991);
38. Horneff, G., et al., "Treatment of Rheumatoid Arthritis with an Anti-CD4 Monoclonal Antibody," *Arthritis & Rheumatism*, 34(2):129-140 (1991);
39. Kalden, J.R., and Manger, B., "Biologic Agents in the Treatment of Inflammatory Rheumatic Diseases," *Curr. Opin. Rheum.* 7:191-197 (1995);
40. Kalden, J.R., and Manger, B., "Biologic Agents in the Treatment of Inflammatory Rheumatic Diseases," *Curr. Opin. Rheum.*, 9:206-212 (1997);
41. Kavanaugh, A., et al., "Anti-TNF- α Monoclonal Antibody (mAb) Treatment of Rheumatoid Arthritis (RA) Patients With Active Disease On Methotrexate (MTX); Results of a Double-Blind, Placebo Controlled Multicenter Trial," *Arth. Rheum.*, 39 (Suppl. 9):18-22 (October 1996), Abstract 575;
42. Kozarek, R.A., et al., "Methotrexate Induces Clinical and

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43. Maini, R.N., et al., "Clinical Response of Rheumatoid Arthritis (RA) to Anti-TNF α (cA2) Monoclonal Antibody (mab) is Related to Administered Dose and Persistence of Circulating Antibody," *Arth. Rheum. Supplement*, 38(9):S186 (1995); Abstract 200;
44. Maini, R.N., "The Role of Cytokines in Rheumatoid Arthritis," *J. Royal College of Physicians of London*, 30(4):344-351 (1996);
45. Manual of Medical Therapeutics, 25th Edition, Orian et al., (editors), Dept. of Medicine, Washington University, St. Louis, MO, Pages 308-309 (1986);
46. Markowitz, J., et al., "Immunology of Inflammatory Bowel Disease: Summary of the Proceedings of the Subcommittee on Immunosuppressive Use in IBD," *Journal of Pediatric Gastroenterology and Nutrition*, 12(4):411-423 (1991);
47. Natanson, C. et al., "Selected Treatment Strategies for Septic Shock Based on Proposed Mechanisms of Pathogenesis," *Ann. Int. Med.*, 120(9):771-783 (1994);
48. Pascalis, L., et al., "Longterm Efficacy and Toxicity of Combined Cyclosporine A-Steroid-Methotrexate Treatment in Rheumatoid Arthritis," *Rev. Esp. Rheumatol.*, 20 Suppl. 1:148

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(1993), Abstract 319;

49. Paul, W.E., ed., *Fundamental Immunology*, 3rd edition (NY: Raven Press) page 242 (1993);
50. Paul, W.E., ed., "Tumor Necrosis Factor," In *Fundamental Immunology*, 3rd edition (NY:Raven Press), pages 807-812 (1993);
51. Racadot, E., "Immunological Follow-up of 17 Patients with Rheumatoid Arthritis Treated in vivo with an Anti-T CD4+ Monoclonal Antibody (B-F5)," *Clinical and Experimental Rheumatology*, 10:365-374 (1992);
52. Ralph, P., "Clinical and Preclinical Studies Presented at the Keystone Symposium on Arthritis, Related Diseases, and Cytokines," *Lymphokine and Cytokine Research.*, 12(4):261-263 (1993);
53. Rankin, E.C.C., et al., "The Therapeutic Effects of an Engineered Human Anti-Tumour Necrosis Factor Alpha Antibody (CDP571) in Rheumatoid Arthritis," *British J. Rheumatology*, 34: 334-342 (1995);
54. Schact, E., "Gegenwärtige und Zukünftige Therapiestrategien der Rheumatoiden Arthritis (RA)," ["The Current and Future Therapy Strategies of Rheumatoid Arthritis (RA)"], *Zeitschrift für Rheumatologie*, 52(6):365-382 (1993);
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(anti-CD4 and anti-interleukin-2 receptor) Combined with Cyclosporin A has a Positive but not Simple Dose-Dependent Effect on Rat Renal Allograft Survival," *Scandinavian J. Immunol.*, 34(5):627-633 (1991);

56. Van Der Lubbe, P.A., et al., "A Randomized, Double-Blind, Placebo-Controlled Study of CD4 Monoclonal Antibody Therapy in Early Rheumatoid Arthritis," *Arth. Rheum.*, 38(8):1097-1106 (1995);
57. Van Dullemen, H.M., et al., "Treatment of Crohn's Disease with Anti-Tumor Necrosis Factor Chimeric Monoclonal Antibody (cA2)," *Gastroenterology*, 109(1):129-135 (1995);
58. Watts, R.A., and Isaacs, J.D., "Immunotherapy of Rheumatoid Arthritis," *Annals Rheumatic Diseases*, 51:577-579 (1992);
59. Williams, R.O., et al., "Successful Therapy of Collagen-Induced Arthritis with TNF Receptor-IgG Fusion Protein and Combination with Anti-CD4," *Immunology*, 84:433-439 (March 1995); and
60. Williams, R.O., et al., "Synergy Between Anti-CD4 and Anti-Tumor Necrosis Factor in the Amelioration of Established Collagen-Induced Arthritis," *Proc. Natl. Acad. Sci. USA*, 91:2762-2766 (1994).

Each of the above-listed publications is listed again on the accompanying PTO Form 1449 (**Exhibit A**).

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Applicants request that the Examiner review the publications and make them of record in the subject application.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with the filing of this Information Disclosure Statement. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:

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Date

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Serial No.

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INFORMATION DISCLOSURE CITATION
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Applicants

Marc Feldmann et al.

Filing Date

August 3, 2001

Group

Not yet known

U.S. PATENT DOCUMENTS

Examiner Initial								Date	Name	Class	Subclass	Filing Date if Appropriate
		6	0	1	5	5	5	7	01/18/00	Tobinick et al.		
		6	1	9	0	6	9	1	02/20/01	Mak		
		6	1	7	7	0	7	7	01/23/01	Tobinick		
		5	7	9	5	9	6	7	08/18/98	Aggarwal et al.		
		5	9	5	8	4	1	3	09/28/99	Anagnostopoulos et al.		
		5	6	5	6	2	7	2	08/12/97	Le et al.		
		5	7	4	1	4	8	8	04/21/98	Feldmann et al.		
		5	6	9	8	1	9	5	12/16/97	Le et al.		
		5	9	1	9	4	5	2	07/06/99	Le et al.		
		5	3	1	7	0	1	9	05/31/94	Bender et al.		
		5	6	7	2	3	4	7	09/30/97	Aggarwal et al.		

FOREIGN PATENT DOCUMENTS

									Date	Country	Class	Subclass	Translation	
													Yes	No
		WO	0	0	5	0	0	7	9	08/31/00	PCT			
		WO	8	9	0	8	4	6	0	09/21/89	PCT			
		WO	9	2	0	8	4	7	4	05/29/92	PCT			
		WO	9	2	0	7	5	8	5	05/14/92	PCT			
		WO	9	2	1	6	5	5	3	10/01/92	PCT			
		WO	9	5	0	9	6	5	2	04/13/95	PCT			
		WO	9	6	3	3	2	0	4	10/24/96	PCT			
		WO	9	8	2	4	4	6	3	06/11/98	PCT			

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

		Barrera, P., et al., "Effects of a Weekly Dosis of Methotrexate on IL-1 TNF and IL-6 in patients with Rheumatoid Arthritis," <i>Cytokine</i> , 3 (5) :504, Abstract 330 (1991).
		Bologna, C., and Sany, J., "Association des Traitements de Fond dans la Polyarthrite Rhumatoide," <i>Presse Med.</i> , 25:876-878 (1996).
		Borigini, M.J., and Paulus, H.E., "Combination Therapy," <i>Baillière's Clin. Rheum.</i> , 9 (4) :689-710 (1995).

EXAMINER

DATE CONSIDERED

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Applicants: Marc Feldmann et al.
Serial No.: 09/921,937
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Exhibit A

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APPLICANT

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